

Early phase clinical trials of anticancer agents in children and adolescents — an ITCC perspective

Moreno, Lucas; Pearson, Andrew D J; Paoletti, Xavier; Jimenez, Irene; Geoerger, Birgit; Kearns, Pamela R; Zwaan, C Michel; Doz, Francois; Baruchel, Andre; Vormoor, Josef; Casanova, Michela; Pfister, Stefan M; Morland, Bruce; Vassal, Gilles; Innovative Therapies for Children with Cancer (ITCC) Consortium

DOI:

[10.1038/nrclinonc.2017.59](https://doi.org/10.1038/nrclinonc.2017.59)

License:

None: All rights reserved

Document Version

Peer reviewed version

Citation for published version (Harvard):

Moreno, L, Pearson, ADJ, Paoletti, X, Jimenez, I, Geoerger, B, Kearns, PR, Zwaan, CM, Doz, F, Baruchel, A, Vormoor, J, Casanova, M, Pfister, SM, Morland, B, Vassal, G & Innovative Therapies for Children with Cancer (ITCC) Consortium 2017, 'Early phase clinical trials of anticancer agents in children and adolescents — an ITCC perspective', *Nature Reviews Clinical Oncology*, vol. 14, pp. 497–507. <https://doi.org/10.1038/nrclinonc.2017.59>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Title:

Early phase clinical trials of anticancer agents in children and adolescents: an Innovative Therapies for Children with Cancer (ITCC) position paper

Authors:

Lucas Moreno (1)*; Andrew DJ Pearson (2,3)*^; Xavier Paoletti (4); Irene Jimenez (5); Birgit Geoerger (6); Pamela R Kearns (7); C Michel Zwaan (8); Francois Doz (5); Andre Baruchel (9); Josef Vormoor (10); Michela Casanova (11); Stefan M. Pfister (12); Bruce Morland (13); Gilles Vassal (14)

Affiliations

1. CNIO-HNJ Clinical Research Unit - Paediatric Phase I-II Clinical Trials Hospital Infantil Universitario Niño Jesús, , Madrid, Spain
2. Paediatric Drug Development, Children and Young People's Unit, The Royal Marsden NHS Foundation Trust, Sutton, SM2 5PT, UK
3. Division of Clinical Studies and Cancer Therapeutics, The Institute of Cancer Research, Sutton, SM2 5NG, UK
4. Biostatistics and Epidemiology, INSERM U1018, Gustave Roussy, Paris, France
5. Department of Paediatric, Adolescents and Young Adults Oncology, Institut Curie, Paris and University Paris Descartes, France
6. Department of Pediatric and Adolescent Oncology, CNRS UMR 8203 Vectorology and Anticancer Treatments, Gustave Roussy, Univ. Paris-Sud, 94805 Villejuif, France;
7. Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK
8. Dept. of Pediatric Oncology/Hematology, Erasmus MC/Sophia Children's Hospital, 3015 GJ Rotterdam, The Netherlands
9. Department of Pediatric Hematology, Hôpital Robert Debré, AP-HP and University Paris Diderot, Paris, France
10. Wolfson Childhood Cancer Research Centre, Northern Institute for Cancer Research, Newcastle University and Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
11. Paediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
12. German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK) and Heidelberg University Hospital, Heidelberg 69120, Germany
13. Department of Paediatric Oncology, Birmingham Children's Hospital, Birmingham, UK
14. Department of Clinical Research, Gustave Roussy, Paris-Sud University, Paris, France

* These authors contributed equally

^Retired

Corresponding author:

Prof. Andrew DJ Pearson

Email: andy1pearson@btinternet.com

Summary

The paradigm shift in adult oncology drug development has not been translated into drug development for children with cancer. Early phase clinical trial designs for molecularly targeted agents and immunotherapeutics in paediatric malignancies need to be adapted to this landscape. This article describes the strategy of the Innovative Therapies for Children with Cancer Consortium for conducting early phase trials with these new agents.

Therapeutic need, tumour biology and a drug's mechanism of action (MoA) drive prioritisation of drug development. Early phase paediatric trials should be biologically driven and molecular profiling is very strongly encouraged. Uninterrupted recruitment and extrapolation from adult studies when possible is ideal. If a drug has neither serious, dose-related toxicities nor a narrow therapeutic index then studies should generally start at the adult recommended phase II dose corrected for body surface area and act as dose confirmation studies. These trials should encompass expansion cohorts providing further data on toxicity, pharmacokinetics, pharmacodynamics and importantly activity. With adaptive trial designs, promising drugs can rapidly progress to randomised studies. Pharmacology in young children and developmental toxicities can be addressed in subsequent studies. This model, together with MoA drug development, will substantially accelerate drug development for children and adolescents with cancer.

Introduction

Introducing novel drugs, molecularly targeted agents and immunotherapeutics, into front-line treatment for paediatric malignancies is essential to improve outcomes for children and adolescents with cancer. There is a major unmet need for new therapies as thousands of children with cancer still die from their disease¹ and for a significant proportion of survivors long-term sequelae from current treatments are significant². New drugs need to be efficiently and rapidly evaluated and the appropriate dose, schedule, toxicity profile, pharmacological properties and efficacy determined. Progress will be fragmented and slow unless there is an agreed process for this assessment. Novel anti-cancer drugs comprise different agents including small tyrosine kinase inhibitors, drugs focussing on epigenetic alterations, immune checkpoint inhibitors and monoclonal antibodies³. The goal is to achieve a comprehensive therapeutic approach integrating drugs against cancer vulnerabilities with inhibitors against genomic drivers, immune responses or epigenetic alterations⁴.

In 1998 a consensus paper on the conduct of phase I studies for children with cancer was published by international investigators in paediatric oncology drug development⁵. This manuscript reported the methodology for the paediatric evaluation of cytotoxic agents in common usage at that time and these principles are now utilised in early clinical trials for paediatric cancer. However, in the experience of the Innovative Therapies for Children with Cancer (ITCC) Consortium of 51 Paediatric Oncology centres in 12 European countries and Israel⁶, the methodology described in 1998 is not applicable in the modern era of targeted therapies and immunotherapeutics. Its use results in significant delays in the evaluation of new anti-cancer drugs in children and increased risk of giving a non-active dose, without serving the methodology's purpose of reducing the risks associated with early clinical trials. It is therefore time to consider a new consensus on the conduct of early clinical trials of targeted drugs for children with cancer.

The complexities of drug development for adult cancers have significantly increased with the large number of meaningful molecular subtypes of most tumours and the advent of combination therapies, companion diagnostics and immunotherapeutics. Nevertheless, the number of molecularly targeted agents being evaluated each year has grown exponentially⁷. As of July 2016, more than 70 molecularly targeted agents have been approved by the Food and Drug Agency (FDA) and European Medicines Agency (EMA) for adult cancers, but to date only imatinib for chronic myeloid leukaemia (CML), everolimus for subependymal giant cell astrocytoma and dinutuximab for neuroblastoma have been approved for childhood cancers^{8,9}. Furthermore, despite the change in landscape of adult oncology with "precision medicine", there is a paucity of new drugs being

integrated into paediatric phase III trials, and molecularly targeted agents have not been introduced into front-line therapy for many poor prognosis paediatric malignancies.

However, new drugs directed against specific cancer targets are increasingly available for paediatric use, for example, inhibitors of BCR-ABL, anaplastic lymphoma kinase (ALK) and BRAF and bispecific T-cell engager (BiTE). It is essential that the design of first-in-child trials is adapted to facilitate these new agents being more efficiently evaluated while maintaining safety. Alternative approaches are needed to those required with cytotoxic drugs with treatment needing to be matched to the molecular characteristics of the tumour. Molecularly targeted agents have different toxicity profiles to cytotoxics, with non-haematological toxicity being predominant; their efficacy generally does not increase with dose and their therapeutic index is wider. In addition, it is important that all eligible patients who wish to receive these new drugs are offered the opportunity to participate in clinical trials, giving children and adolescents with relapsed disease more therapeutic options.

Major changes have occurred in relation to paediatric early phase clinical trials and there is a new environment for cancer drug development in children. Globally all stakeholders (academia, the pharmaceutical industry, parents, patient advocates, regulatory agencies, public health agencies, research-funding agencies and philanthropic organisations) are working closely together^{10,11}. On both sides of the Atlantic, new regulations, which aim to encourage the interest of industry in paediatric studies, have been implemented, including the European Paediatric Medicine Regulation EC No. 1901/2006 and, in the US, the Best Pharmaceuticals for Children Act (BPCA), the Paediatric Research Equity Act (PREA), and the Creating Hope Act¹²⁻¹⁵.

Current process for evaluation of new anti-cancer drugs in children

As paediatric drug development is still largely centred on adult conditions, with the exception of anti-GD2 targeted therapies for neuroblastoma¹⁶, the majority of drugs that reach paediatric clinical development have already been extensively explored in adult trials. Despite the regulatory and scientific motivation to commence first-in-child studies at completion of first-in-man trials, in reality, paediatric phase I trials generally start after pivotal phase III studies are near completion in adults, thereby delaying children's access to these new drugs substantially.

Traditional practice has been that all drugs evaluated in children have to go through a dose escalation phase, using methods such as 3+3¹⁷ or the rolling six¹⁸, with multiple dose levels until a maximum tolerated dose (MTD) and recommended phase II dose (RP2D) are identified. The starting

dose for this dose escalation has conventionally been 80% of the adult RP2D⁵. Classic dose escalation designs were developed for cytotoxic drugs where the main toxicities are dose-related (i.e., haematological toxicities), and their main objective was to prevent and limit severe toxicities by only allowing small groups of patients to receive increasing doses of the agent(s). This approach, although successful with some drugs, sometimes has resulted in long phase I trials, with many dose levels, multiple episodes of suspended recruitment whilst patients waited for assessment for dose limiting toxicity (DLT) evaluation, and the requirement for large numbers of patients (Table1). Hence, for targeted drugs the use of this classic dose escalation model based on the identification of DLTs and definition of an MTD has slowed progress while not resulting in an enhanced protection against undesirable side effects.

Following on from phase I studies, the tradition has been to evaluate activity in single arm phase II studies and then in different relapsed strategies before reaching front-line trials.

Disadvantages of the current process for evaluation of new anti-cancer drugs in children

In addition to drug development being largely driven by the availability of drugs developed or marketed for adults, rather than mechanism of action (MoA)²⁰, the current process for evaluation of new anti-cancer drugs is not suitable for paediatric studies of molecularly targeted agents and immunotherapeutics for two main reasons. First, for molecularly targeted drugs, most toxicities are not necessarily dose-related but class-related. Tolerable paediatric doses will likely be equivalent to the adult ones corrected for body surface area (BSA), which results in the same pharmacokinetic values of area under the concentration time curve and trough levels as the adult doses. In a published analysis of the paediatric MTD for all 25 molecularly targeted agents approved by the FDA or EMA up to 2012, we demonstrated that for 75% of molecularly targeted agents, the established paediatric RP2D was between 90% and 130% of the BSA-adjusted approved dose in adults. Significantly, this report also showed that for molecularly targeted agents, toxicities seen in paediatric studies were those seen in adults and main pharmacokinetic parameters in children were comparable with those observed in adults^{21,22}. The only drug in the 25 where DLT was observed in children at lower dose levels than in adults was sunitinib. The main toxicities differed too, despite similar pharmacokinetic parameters, myelosuppression and transaminase elevations were the most commonly reported toxicities in children compared to fatigue and gastrointestinal symptoms in adults. The mechanism for this is uncertain, however, children have tolerated higher doses and a large percentage of adults on sunitinib undergo dose reductions with cumulative dosing. Furthermore, the choice of paediatric population – heavily pre-treated children with relapsed/

refractory solid tumours – might have contributed to this finding^{23,24}. Thus paediatric dosing can begin at the adult RP2D (adjusted for BSA) for some targeted agents for which the adult RP2D is not based on toxicity and is below the MTD.

A further consideration is that molecularly targeted agents are evaluated in the paediatric population at doses below those already established to be active in adults, raising ethical concerns, as therapeutic intent is central to studies in children²⁵. The paediatric starting dose for most agents should be an equivalent dose of the minimum active target exposure.

Amongst the challenging areas in paediatric drug development are pharmacological differences and developmental toxicities in children less than three years of age²⁶. The small number of infants and young children participating in early clinical trials poses practical difficulties in addressing pharmacokinetic differences at each dose level, or even during the whole dose escalation trial. In a recent report from eight large ITCC centres, only 9 of 270 (3.3%) patients participating in dose determining trials were below 3 years of age²⁷. Moreover, evaluation of developmental toxicities requires longer survival and follow up, so these would generally be studied in late stage or upfront trials, although for some very active agents, data on developmental toxicities should also be collected in early phase trials²⁸.

In summary, trial designs that require systematic dose escalations are not efficient for paediatric development for molecularly targeted drugs and immunotherapeutics. They add unnecessary time to the duration of studies and require some patients to be treated at doses lower than the adult MTD/RP2D, while at the same time not protecting paediatric patients from unacceptable, unexpected or paediatric-specific toxicities.

Objectives of first-in-child studies

The main aim of first-in-child studies is to determine the toxicity profile and the RP2D and schedule for further evaluation of a new drug. The RP2D may also take into account available data about the toxicity profile measured at all treatment cycles (and not only at the first treatment cycle), pharmacokinetics, pharmacodynamic (target inhibition) biomarkers and preliminary data about activity. For a number of drugs the MTD is not required as a biological effect can be obtained with doses below the MTD where biological effect has guided the paediatric RP2D. With targeted drugs it is not necessary to escalate the dose to an MTD, but rather a RP2D can be based on an integration of

available adult, toxicity, activity and biomarker data. Much of this information can be extrapolated from adult studies²⁹ and will be obtained in later phases of the development of the drug.

Initial dose for first-in-child early clinical trials

As mentioned, a publication analysing 19 paediatric dose finding trials of molecularly targeted agents found that the paediatric RP2D of molecularly targeted agents ranged between 90% and 130% of the BSA adjusted approved dose in adults for most drugs, and often based on pharmacokinetic and pharmacodynamic end points in the absence of DLT²¹. This, taken together with the fact that the short-term safety profiles and DLT described in paediatric phase I trials are similar to those reported in the adult population, means that identifying toxicity that has not been documented in adults previously is very rare. Furthermore, 25% of paediatric dose finding trials of molecularly targeted drugs never identify an MTD due to absence of DLT.

If the toxicity profile and the pharmacokinetic parameters observed in children treated at the adult RP2D are similar to those in adults, escalating to the MTD is not necessarily required, unless a dose-activity relationship has been documented in adults. Therefore, we recommend that where possible paediatric first-in-child studies of molecularly targeted agents should start at 100% of the BSA adjusted equivalent approved RP2D for exposure in adults (Figure 1). There are specific situations where the benefit/risk ratio should be weighed against this recommendation. In cases of specific, serious, dose-related toxicities or a narrow therapeutic index, dose escalation should start at 80% of the adult RP2D and escalate to 100% and 120% if indicated (Figure 1). In this context we define therapeutic index as the ratio of the highest exposure to the drug that results in no toxicity to the exposure that produces the desired efficacy³⁰. This recommendation is supported by the ITCC experience since 2003 across 25 dose finding trials, together with a systematic review of paediatric dose finding studies conducted for all molecularly targeted drugs approved for adult cancer indications up to 2012²¹. This experience shows that for molecularly targeted drugs, starting at lower doses is not useful in preventing severe toxicities.

The proposed approach aims to maximise the information from adult studies and extrapolate from existing data where possible, as supported recently by the EMA²⁹. This extrapolation is very feasible for studies of molecularly targeted drugs for conditions that occur both in adults and children (such as CML) and when there are shared common molecular aberrations (such as BRAF mutated cancers – melanoma and high grade glioma³¹). Therefore for many drugs with a wide therapeutic index, only a dose confirmation study will be required with a limited sample size. For instance, analysis of ten

patients would generally limit the risk of missing adverse events with a 33% (or more) prevalence, corresponding to a futility analysis for a 30% activity rate target or more and allow for estimation of key pharmacokinetic parameters, providing that the pharmacokinetic population model is known from adults³²; and if the safety profile and pharmacokinetics are equivalent to those in adults, the paediatric RP2D can be determined (Figure 1). Escalating up to the MTD in children if this dose is higher than the RP2D is then not necessary. Small studies can provide sufficient information to proceed to later stages of development to define activity/efficacy, as exemplified by recent studies with nilotinib³³.

Most monoclonal antibodies do not generally require a dose escalation study, for example, brentuximab for CD30+ lymphomas^{34, 35} and antibodies against insulin-like growth factor receptor 1³⁶⁻⁴⁰, which only required small dose confirmation studies. In general, if the adult RP2D is not based on toxicity and is below the adult MTD, then paediatric dosing can begin at the adult RP2D adjusted for BSA regardless of agent class.

In the absence of particular safety issues, designs that remain closed for a significant part of the time should not be employed, since they pose an additional burden for patients and parents waiting for trial allocations. Uninterrupted recruitment is a priority as soon as deemed safe (e.g., after the first dose level or cohort of patients is analysed).

If a drug has specific, serious, dose-related toxicities or a narrow therapeutic index, such as blinatumomab (with a high tumour burden), moxetumomab or EGFR inhibitors⁴¹⁻⁴³, then dose escalation starting from 80% of the adult RP2D is recommended. New dose escalation designs such as the Bayesian logistic regression model (BLRM) or continuous reassessment method (CRM) will maximise the efficiency of the dose escalation. CRM extensions have the advantage of incorporating events after cycle 1, if needed, and of providing a useful tool to monitor the risk of toxicity during the expansion cohort. Several studies, using simulations, have shown the superiority of model-based designs over the 3+3 or the rolling six in the context of paediatric trials⁴⁴⁻⁴⁶. A review of 84 first-in-man, adult phase I trials of single targeted agents found that the number of trials with a median number of dose levels using CRM was almost double the number of trials using the 3+3 method, even though the median number of patients was similar and the number of patients treated at higher doses than the MTD was lower with the CRM than with the 3+3 or the accelerated titration design. To date there have been no such comparisons in paediatric oncology as this is difficult when the choice of method is not independent of the type of agent and the anticipated

number of levels that will be escalated. However, the rolling six would be acceptable if a limited number of dose levels were to be explored and accrual were not too fast; but in this situation, more than 6 patients at the RP2D would be required to evaluate pharmacokinetics. Table 2 provides an overview of different dose escalation methods that could be used for molecularly targeted drugs and Table 3 illustrates recommendations for early phase studies in children based on findings from studies in adults.

Early phase studies should include expansion cohorts

In a homogeneous cohort of patients, expansion cohorts provide additional pharmacokinetic, pharmacodynamic and safety data that are more similar to the phase II setting and can identify early signals of anti-tumour activity⁴⁴. These cohorts aim to enrich the patient population for those tumours (or genomic aberrations) with a maximal probability of response based on molecular characteristics³¹ or to detect first signals in diseases of interest. The size of expansion cohorts can be based on feasibility with statistical calculations that can inform go/no-go decisions⁴⁵. While not definitive, in the context of biomarker-rich trials they can provide very good evidence to support further development of a particular drug. A smaller sample size can be sufficient to validate pharmacokinetic estimates when the population model is known from adults. For drugs with a large therapeutic index, dose confirmation in selected patient populations with given histologies or molecular profiles will allow these patients to be assessed for activity.

It is necessary to define in the study protocols the go/no-go decision rules in the expansion cohorts, particularly if the decision also incorporates signals of activity. Once the RP2D has been determined, expansion cohorts are established in the disease or molecular subtypes in which there is a biological rationale for the drug's MoA or an indication of activity in the dose confirmation/escalation phase. A design with go/no go decision rules based on activity can be applied to the expansion cohort. For instance, we implemented an Ensign 3-stage design⁴⁵ in the multiple agent ITCC European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours (ESMART) study (NCT02813135). In this study, ten patients are recruited at the RP2D including those in the dose confirmation study. If there is no response in the first ten patients, then a further evaluation of the drug is postponed or abandoned. However, if there is a response in the first ten patients, then a further 16 patients are enrolled with one interim analysis and an early stopping rule. The two main advantages of the 3-stage design are that: (i) the 10 patients treated at the RP2D in the dose confirmation (or possibly dose escalation) stage can be evaluated for response and correspond to the first step of the Ensign 3-stage design; therefore this design is driven by statistical

and clinical hypotheses in the decision to move from the dose-confirmation/escalation phase to the expansion cohort; (ii) given the relatively low accrual of paediatric studies, a 3-stage design allows for a more frequent examination of the data and hence the possibility of more rapidly stopping a trial of an inefficient drug. Alternative designs, including Bayesian approaches, are possible as long as they provide reliable data at the end of the trial for starting comparative, practice-changing trials (Figure 1).

For agents targeting specific oncogenic drivers present in the patients' tumours (e.g., BRAF inhibitors for BRAF mutated gliomas or ALK in anaplastic large cell lymphoma [ALCL]) where a predictive biomarker is well defined, a small, enriched expansion cohort will be sufficient to show whether the drug is active in terms of response rate. In contrast, for inhibitors of cell signalling pathways (e.g., MEK or phosphoinositide-3 kinase (PI3K) inhibitors in unselected populations), where a predictive biomarker has not been well defined, expansion cohorts might not be sufficient to show single agent activity. Activity signals may require a combination study and single agent studies may only document inhibition of a pharmacodynamic target in a homogeneous cohort of patients treated at the same dose allowing the drug to progress to a combination study. In the absence of a very strong biomarker and resistance to monotherapies, combinations have to be explored as early as possible to prevent recruiting numbers of patients to single-agent expansion cohorts with a low probability of activity; this approach is being adopted in new trials^{46,47}. The potential activity of the drug as a single agent depends on the drug's mechanism of action. There are some drugs where activity can be expected as a single agent, e.g., targeting a strong oncogenic driver such as BRAF or ALK, but others where a combination study is required. It is not possible to generalise, but it is important not to disregard a drug as a single agent where activity might only be expected in combination with another. The combination of expansion cohorts with a dose confirmation study makes the trials similar to phase I/II trials and we propose these should be termed "early phase clinical trials" (Figure 1, Table 4). An early phase trial has two principle components: i) a dose confirmation or escalation phase in which the toxicity profile and the RP2D and preliminary pharmacokinetics are determined, and ii) expansion cohorts where additional pharmacokinetic, pharmacodynamic and safety data, and importantly early signals of anti-tumour activity, are obtained.

Later phases of development

Success or failure criteria in single arm phase II trials, with a target of a clinically acceptable response rate that would lead to further evaluation of the drug, are always estimations based on historical

data, which often underestimate the true effect of standard treatment⁴⁸; hence, randomised phase II trials are preferred.

Given the rarity of paediatric cancers, novel designs (e.g., Bayesian or a two-stage Minimax Jung designs) can be used to minimise sample size, which can be in the region of 25-35 patients^{49,50}. Randomised phase II trials are feasible designs to evaluate new drugs in the first relapse setting for most poor prognosis paediatric cancers where outcome at first relapse is poor and new drugs are needed. For example, currently there are three ongoing randomised clinical trials, including between 74 to 160 patients, evaluating targeted agents for neuroblastoma across the globe. The International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN)/ITCC BEACON-Neuroblastoma trial is testing three randomised questions (activity of two chemotherapy regimens and role of the anti-VEGF monoclonal antibody bevacizumab), which will allow evidence-based decisions⁵¹. Also COG ANBL1221, a randomized phase II selection design, compared the addition of temsirolimus or dinutuximab plus granulocyte-monocyte colony stimulating factor to an irinotecan/temozolomide backbone in patients with relapsed or refractory neuroblastoma⁵⁰ and made a conclusion with 35 randomised patients. In a GPOH study, the addition of rapamycin and dasatinib to irinotecan/ temozolomide is being compared in a randomised phase II trial⁵². Similar platforms are being developed both sides of the Atlantic for other common tumour types such as Ewing sarcoma⁵³ or rhabdomyosarcoma⁵⁴. For rarer tumour types or those with better outcome, such as acute lymphoblastic leukaemia or Wilms tumour, achieving the required patient numbers poses challenges and supports the need for global studies. Even small, randomised trials provide better evidence than single arm trials⁴⁹. The major advantage of a randomised phase II trial is that it provides more solid evidence of activity compared to single arm trials in which the estimations for considering an agent successful/unsuccessful are based on historical controls. Hence, using randomised phase II trials will eventually result in fewer patients being needed to decide if a drug should or should not be advanced to a phase III trial. Essentially, **only** if initial signals of activity are demonstrated in either a single agent or combination in an expansion cohort of an early phase clinical trial, will that single agent or combination be taken forward to randomised phase II trials. We propose new roles for early phase clinical trials, which would better inform the selection of agents for randomised phase II trials. If a sufficient level of activity is confirmed in a randomised phase II trial, the drug should be taken forward to front-line phase III trials. With this approach drugs can move from first-in-child to front-line trials in only three steps.

The Pharmacological Audit Trail in paediatric cancers

The Pharmacological Audit Trail is a paradigm applied in adult drug development which is being embraced in paediatric early phase studies, including the ITCC ESMART study. This approach, incorporating biological hypotheses into early clinical trials includes a continuous bench-to-bedside and back again strategy with predictive and pharmacodynamic biomarkers, and will accelerate and improve drug development⁵⁵. In parallel, pharmacogenetic studies that explore individual variability of new drug metabolism should be incorporated to paediatric trials.

It is critical that biomarkers⁵⁶ are considered in paediatric early phase clinical trials and that predictive and pharmacodynamic data obtained in trials in adults are applied if relevant in children. Table 4 describes the roles, advantages and disadvantages of types of biomarkers.

Examples of the successful application of the Pharmacological Audit Trail in early phase clinical trials include the COG phase I trial of the AKT inhibitor MK2206, where proof of target inhibition biomarkers [pAkt] demonstrated effective target inhibition at the RP2D⁵⁷. The phase I trial of the aurora kinase inhibitor AT9283 used paired skin punch biopsies to demonstrate aurora kinase inhibition at higher dose levels⁵⁸. In some instances, new biomarker assays relevant to the biology of paediatric tumours will have to be developed and validated in studies in children, for example, for drugs against paediatric-specific targets such as MYCN⁵⁹. Liquid biopsies provide an opportunity to carry out pharmacodynamic studies sequentially in children without tumour biopsies. Also, paediatric studies have used functional imaging as a non-invasive biomarker to avoid repeat tumour biopsies; for example, dynamic contrast-enhanced magnetic resonance imaging in the study of pazopanib⁶⁰ and tumour perfusion assessed by magnetic resonance imaging in the study of vandetanib⁶¹. Extrapolation from adult, post-treatment pharmacodynamic data (with confirmation of comparable pharmacokinetics in adults and children) should be considered.

When a predictive or pharmacodynamic biomarker for a targeted agent has not yet been found to correlate with the drug's activity, exploration of this relationship could continue during later stages of the drug's development. Similarly, a biomarker that has been identified as an exploratory endpoint of an early phase trial should be confirmed in later stages of development.

Genomic studies of tumour

Availability of tumour material at the time of enrolment in an early phase trial will enable the maximal knowledge to be obtained from the study. Although relevant for some characterisations,

tumour from an earlier presentation is typically inappropriate, as it is well documented that clonal evolution occurs in the vast majority of cases⁶²⁻⁶⁴; in addition tumour heterogeneity also has to be considered. The use of liquid biopsies, e.g., circulating free DNA⁶⁵, which are collected sequentially during an early phase trial, is a promising approach being applied in paediatric cancers. ITCC and other initiatives are now in place to routinely molecularly profile tumours at relapse (MOlecular Screening for CAncer Treatment Optimization [MOSCATO-01]⁶⁶, Proof-of-Concept Study To Stratify Targeted Therapies Adapted To Molecular Profiling [MAPPYACTS], Individualized Therapy for Relapsed Malignancies in Childhood [INFORM]⁶⁷, Individualised Therapy [iTHER], Stratified Medicine – Paediatrics [SM-PAEDS], NCI-COG Pedi-MATCH⁶⁸, iCAT⁶⁹). As well as generating hypotheses regarding the evolution of the tumour and tumour heterogeneity, these protocols will determine if actionable mutations are present at relapse, thereby identifying potential molecularly targeted drugs that could be utilised in a stratified, precision medicine strategy with molecular enrichment and predictive biomarkers. However, the need for tumour sampling immediately prior to study entry needs to be placed within the context of the agent being studied, the objectives of the clinical trial, the ethical justifications for tumour sampling, and the clinical status of the patient population being studied.

Infants and very young children (<2 years of age)

It is known that renal and hepatic functions are significantly different in children younger than 3 years of age⁷⁰ and drug metabolism and pharmacokinetic profiles can differ significantly in younger cohorts. Thus collection of pharmacokinetic data in younger children is required, particularly for those agents focussing on malignancies occurring at younger ages, such as rhabdoid tumours or infant leukaemias. However, since relapsed cancers are rare in this population, a pre-specified number of infants should not be pre-defined in the early phase trial protocol. Pharmacokinetic data in infants should be collected also during the expansion cohort or subsequent studies. Hence, trials of anticancer agents should not be stratified in age cohorts.

Adolescents

Although not based on medical or biological grounds, the upper age for “paediatric” early phase clinical trials is often below 18 years, which is also the lower age for many adult phase I studies. While it is understandable that there is a distinction between paediatric and adult populations, studies should be adapted to the population of interest. Hence, a first-in-child early phase study with the objective of defining a “paediatric” dose and pharmacokinetic profile should concentrate on children and adolescents. However, this 18-years “boundary” should not limit the access of

adolescents (12-17 years old, according to the International Conference on Harmonization [ICH] E11) to early trials of new anti-cancer agents of interest.

The pharmacokinetic, pharmacodynamic and toxicity profiles of drugs are very likely to be similar in adolescents to the adult population⁷¹. In cases with a significant biological rationale or conditions that overlap between adolescents and young adults, such as Ewing sarcoma, Hodgkin lymphoma, high-grade glioma, soft tissue sarcoma and osteosarcoma, adolescents have been allowed in adult phase I studies. This is a valid means to accelerate drug development for this population while at the same time ensuring that the population of interest is well represented. For example, adolescents older than 12 years with Ewing or other sarcomas were included³⁶ in phase I trials of anti-IGF-1R monoclonal antibodies and trials of the mTOR/DNA-PK inhibitor CC-115 included an expansion cohort with Ewing sarcoma including adolescents⁷², as did studies in melanoma⁷³ and ALK-positive diseases (CREATE)⁷⁴. Building on this approach, it is proposed that where the MoA of the drug is relevant, adolescent patients should be included in “adult” phase I trials after the dose escalation phase is completed and this should complement paediatric evaluation. We propose that adolescents can still be included in paediatric phase-I, II and III trials to provide additional therapeutic opportunities and young adult patients can participate in paediatric phase II and III trials, especially when their diagnosis is of a more paediatric type cancer (e.g., medulloblastoma).

Some adult cancers are rare in the paediatric population and occur infrequently in adolescents (e.g., metastatic melanoma or thyroid cancer). When a drug developed for the adult condition is to be evaluated in children and adolescent patients with the same condition possibly at the same time point as in adults, the objective is to demonstrate that the drug has similar toxicity, pharmacokinetics and pharmacodynamic profiles in children and adolescents compared to adults and hence, a dose confirmation, not a dose escalation study, is required. Pharmacokinetic modelling is a useful tool to improve and reduce the required sample size.

In many instances, an adult condition might be rare in children and adolescents but the drug might be relevant for other paediatric cancers. A MoA, drug development approach focusing not on diseases, but on targets present in different diseases with a higher frequency in children, would overcome these challenges²⁰. Together these strategies would facilitate access to new drugs and provide more options for adolescent patients.

Late toxicities and long-term follow up

Concerns about late toxicities in children, affecting areas such as growth, development or neurocognition, might arise with new molecularly targeted agents and these cannot be appropriately addressed in first-in-child studies. However, toxicity data beyond the first cycle and in surviving patients should still be collected. In cases with specific concerns, appropriate monitoring (e.g., bone age, growth plate or dental studies) should be implemented when relevant. For example, several anti-angiogenic agents have been evaluated in paediatric patients, but only with specific VEGF/VEGFR blocking agents (sunitinib or pazopanib) were alterations of the growth plate described during the phase I trial. As a result, to provide further insight, increased monitoring for bone and musculoskeletal growth has been incorporated into ongoing phase II trials for bevacizumab and pazopanib. The true long-term impact of these changes will however only be evaluated when these agents have advanced to front-line studies and when larger populations, including long-term survivors, are available for evaluation. A further example occurred with sonic hedgehog inhibitors vismodegib and sonidegib, which were shown to cause irreversible closure of growth plates⁷⁶ in animal models, however first-in-child trials have not confirmed this^{77,78} and data from phase II trials are awaited⁷⁹. Finally, long-term growth delay has been reported after the chronic use of the tyrosine kinase inhibitor imatinib⁸⁰. Such toxicities can only be identified after long-term surveillance and possibly prolonged use of the drugs, and therefore, will not be easily identified during early clinical trials but during late trials or the post-marketing authorisation phase. Early clinical trials must take into account anticipated life expectancy and consider the balance between incorporating rigorous assessments to detect emerging toxicities and being too burdensome for study participants.

The long-term tolerance of new drugs assumes an even greater importance in children when cancer becomes a more chronic disease (CML is the prime example) and growth retardation has been reported with some BCR-ABL tyrosine kinase inhibitors; this could influence which drug to use within the same class of inhibitors⁸¹. Similarly late sequelae are of great relevance in new drugs for a good prognosis malignancy, e.g., BRAF or MEK inhibitors for low grade gliomas, where efficient second line chemotherapy regimens with known late effects are available, but new drugs are needed.

Collaboration with survivorship programmes, for example Pan Care (Pan-European Network for the Care of Survivors after Childhood and Adolescent Cancer), provides an optimal approach⁸². A Working Group of ACCELERATE, the Paediatric Oncology Platform¹⁰, is implementing long-term follow up measures for children and adolescents receiving new anti-cancer drugs.

Conclusion

The landscape in which drug development for paediatric cancers takes place has changed significantly over the last 15 years. Methodological aspects of new drug development must adapt to this new landscape, providing more efficient results and best answers to specific ethical issues⁸³. Molecularly targeted agents and immunotherapeutics require a new paradigm of drug development with selection of drugs based on MoA and tumour biology²⁰. In parallel to this approach in selecting new agents, drugs should be evaluated in early phase clinical trials with dose confirmation studies at the adult RP2D adjusted for BSA with expansion cohorts that integrate activity and biomarker endpoints to address biological hypotheses. In many instances the aim is to validate the use of the adult dose in paediatrics, therefore extrapolation of data from adult studies should be undertaken at every opportunity. If the drug has specific, serious, dose-related toxicities or a narrow therapeutic index, then dose escalation studies should be undertaken starting at 80% of the adult RP2D but increasing the trial efficiency by using new dose escalation models such as CRM or BLRM. Expansion cohorts can give preliminary signals of activity determining which drugs should be evaluated further in randomised multi-arm or umbrella matrix studies. By these means drugs can move from first-in-child to front-line trials in just three steps. Very importantly as therapeutic intent is key to the design of early phase studies in children, these recommendations maintain safety and activity as objectives, while minimising the use of protracted phase I trials. The probability of overdosing or under-dosing will be reduced with increased chances that patients are treated at optimum therapeutic doses. This approach is ethically desirable when evaluating drugs in children for which an active dose has already been established in adults and is being applied in ESMART.

Many recently developed adult cancer agents do not target childhood cancers because the genetic and epigenetic repertoire of driver mutations in specific childhood malignancies differs from more common adult-type malignancies. Therefore, there is currently a paucity of targeted cancer drugs addressing paediatric cancer oncogenic drivers. Developing drugs to target driver mutations in childhood malignancies is another key challenge of successfully applying precision medicine principles in paediatric oncology.

A MoA model of drug development alongside innovatively and rationally designed early phase studies will radically accelerate development of anti-cancer drugs for children and adolescents.

Acknowledgements

LM was funded by the Oak Foundation. ADJP was funded through a Cancer Research UK Life Chair and Programme Grant included within a Cancer Research UK ICR Core Award (C347/A15403) and is supported by the NIHR RM/ICR Biomedical Research Centre. MZ is supported by a KiKa-foundation (project 113) grant. We thank Maren White for editorial support in the preparation of this article and Gynette Cook for administrative assistance.

References

- 1 Pritchard-Jones, K., Sullivan R., Children with cancer: driving the global agenda. *Lancet Oncol.* **14**, 189-91 (2013).
- 2 Skinner, R., Wallace, W.H.B., Levitt, G.A., on behalf of the UK Children's Cancer Study Group (UKCCSG) Late Effects Group (LEG). Long-term follow-up of people who have survived cancer during childhood. *Lancet Oncol.* **7**, 489-498 (2006).
- 3 Di Martino, S. et al. Overview of FDA-approved anti cancer drugs used for targeted therapy, *World Cancer Research Journal.* **2**, e553 (2015).
- 4 Hanahan, D., Weinberg, R.A. Hallmarks of cancer: the next generation. *Cell.* **144**,646-74 (2011).
- 5 Smith, M. et al. Conduct of phase I trials in children with cancer. *J Clin Oncol.* **16**, 966-78 (1998).
- 6 Zwaan, C.M. et al. The role of the 'innovative therapies for children with cancer' (ITCC) European consortium. *Cancer Treat Rev.* **36**, 328-34 (2010).
- 7 PhRMA. PhRMA Medicines in Development 2012 Report. 2012. <http://www.phrma.org/sites/default/files/1000/phrmamedicinesindevelopmentcancer2012.pdf>
- 8 Vassal, G., Geoerger, B., Morland, B. Is the European pediatric medicine regulation working for children and adolescents with cancer? *Clin Cancer Res.* **19**, 1315-25 (2013).
- 9 National CancerInstitute. Targeted Cancer Therapies. 2014. <http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted> (accessed 10 June 2016).
- 10 Vassal, G. et al. Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. *Eur J Cancer.* **51**, 218-24 (2015).
- 11 Vassal, G. et al. New drugs for children and adolescents with cancer: the need for novel development pathways. *Lancet Oncol.* **14**, e117-24 (2013).
- 12 Vassal, G. Will children with cancer benefit from the new European Paediatric Medicines Regulation? *Eur J Cancer.* **45**, 1535-46 (2009).
- 13 Rocchi, F. et al. The European paediatric legislation: benefits and perspectives. *Ital J Pediatr.* **36**, 56 (2010).
- 14 Vassal, G., Blanc, P., Pearson, A. Need for change in implementation of paediatric regulation. *Lancet Oncol.* **14**, 1156-7 (2013).
- 15 PDCO Ca. Guideline on pharmaceutical development of medicines for paediatric use, Committee for Medicinal Products for Human Use (CHMP) and Paediatric Committee (PDCO) of the European Medicines Agency1 August 2013. (accessed 10 June 2016)).
- 16 Yu, A.L. et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med.* **363**,1324–34 (2010).
- 17 Le Tourneau, C., Gan, H.K., Razak, A.R., Paoletti, X. Efficiency of new dose escalation designs in dose-finding phase I trials of molecularly targeted agents. *PLoS One.* **7**,: e51039 (2012).
- 18 Skolnik, J.M., Barrett, J.S., Jayaraman, B., Patel, D., Adamson, P.C. Shortening the timeline of pediatric phase I trials: the rolling six design. *J Clin Oncol.* **26**, 190-5 (2008).

- 19 Jimenez, I., Paoletti, X. Technical Report, Institute Curie, Paris.
- 20 Pearson, A.D. et al., on behalf of Members of Working Group 1 of the Paediatric Platform of ACCELERATE. Implementation of mechanism of action biology-driven early drug development for children with cancer. *Eur J Cancer*.**62**, 124-31 (2016).
- 21 Paoletti, X., Geoerger, B., Doz, F., Baruchel, A., Lokiec, F., Le Tourneau, C. A comparative analysis of paediatric dose-finding trials of molecularly targeted agent with adults' trials. *Eur J Cancer*. **49**, 2392-402 (2013).
- 22 Lee, D. P et al. Pediatric Phase I Trials in Oncology: An Analysis of Study Conduct Efficiency. *J. Clin. Oncol.* **23**, 8431–8441 (2005).
- 23 DuBois, S. G. et al. Phase I and Pharmacokinetic Study of Sunitinib in Pediatric Patients with Refractory Solid Tumors: A Children's Oncology Group Study. *Clin. Cancer Res.* **17**, 5113–5122 (2011).
- 24 Chu, T.F. et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet*.**370**, 2011–9 (2007).
- 25 World Medical Association. World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. *JAMA*.**310**, 2191-2194 (2013).
- 26 Norris, R.E., Adamson, P.C. Challenges and opportunities in childhood cancer drug development. *Nat Rev Cancer*.**12**, 776-82 (2012).
- 27 Carceller, F. et al. Prognostic factors of overall survival in children and adolescents enrolled in dose-finding trials in Europe: an Innovative Therapies for Children with Cancer (ITCC) study. *Eur J Cancer* **67**, 130-140 (2016).
- 28 Zwaan, C.M. et al. Dasatinib in children and adolescents with relapsed or refractory leukemia: results of the CA180-018 phase I dose-escalation study of the Innovative Therapies for Children with Cancer Consortium. *J Clin Oncol.* **31**, 2460-8 (2013).
- 29 EMA/199678/2016 "Reflection paper on extrapolation of efficacy and safety in 4 paediatric medicine development". Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/04/WC500204187.pdf.
- 30 Muller,P.Y, Milton, M.N. The determination and interpretation of the therapeutic index in drug development. *Nat Rev Drug Discov.* **11**,751-61 (2012)
- 31 Kieran, M.W. et al. Complete radiographic responses in pediatric patients with BRAFV600-positive tumors including high-grade gliomas: Preliminary results of an ongoing phase 1/2a safety and pharmacokinetics study of dabrafenib. *J Clin Oncol.* **32**, (5s: suppl abstr 10056) (2014).
- 32 https://www-users.york.ac.uk/~mb55/bsi_study/single_event.pdf
- 33 <https://clinicaltrials.gov/ct2/show/results/NCT01077544>
- 34 Neville, K et al. Phase I/II study of brentuximab vedotin in pediatric patients with relapsed or refractory Hodgkin lymphoma or systemic anaplastic large-cell lymphoma: Interim phase I safety data. *J Clin Oncol.* **31**, (suppl; abstr 10028) (2013).
- 35 Locatelli, F. et al. Phase 1/2 study of brentuximab vedotin in pediatric patients with relapsed or refractory Hodgkin lymphoma or systemic anaplastic large-cell lymphoma: Preliminary phase 2 data for brentuximab vedotin 1.8 mg/Kg in the Hodgkin lymphoma study arm. *Blood*.**122**, 4378 (2013).
- 36 Olmos, D. et al. Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751, 871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study. *Lancet Oncol*.**11**, 129–135 (2010).
- 37 Juergens,H. et al. Preliminary efficacy of the anti-insulin-like growth factor type 1 receptor antibody figitumumab in patients with refractory Ewing sarcoma. *J Clin Oncol.* **29**, 4534-4540 (2011).
- 38 Malempati, S. et al. Phase I/II trial and pharmacokinetic study of cixutumumab in pediatric patients with refractory solid tumors and Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol*.**30**, 256-262 (2012).

- 39 Pappo, A.S. et al. R1507, a monoclonal antibody to the insulin-like growth factor 1 receptor, in patients with recurrent or refractory Ewing sarcoma family of tumors: results of a phase II Sarcoma Alliance for Research through Collaboration study. *J Clin Oncol.* **29**, 4541-7 (2011).
- 40 Frappaz, D. et al. Phase I Study of Dalotuzumab Monotherapy and Combination Therapy Ridaforolimus-Dalotuzumab in Pediatric Patients with Advanced Solid Tumors. *Eur J Cancer.* **62**, 9-17 (2016).
- 41 Zugmaier, G. et al. A Phase 1/2 Study of Blinatumomab In Pediatric Patients With Relapsed/Refractory B-Cell Precursor Acute Lymphoblastic Leukemia. *Blood.* **122**, 70 (2013).
- 42 Wayne, A.S. et al. Pediatric phase 1 trial of moxetumomab pasudotox: Activity in chemotherapy refractory acute lymphoblastic leukemia (ALL). In: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia: AACR; Cancer Res;74(19 Suppl):Abstract nr CT230 (2014).
- 43 Geoerger, B. et al Innovative Therapies for Children with Cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors. *Neuro Oncol.* **13**, 109-18 (2011).
- 44 Onar-Thomas, A., Xiong, Z. A simulation-based comparison of the traditional method, rolling-6 design and a frequentist version of the continual reassessment method with special attention to trial duration in pediatric phase I oncology trials. *Contemp Clin Trials.* **31**, 259–70 (2010).
- 45 Zhao, L., Lee, J., Mody, R., Braun, T.M. The superiority of the time-to-event continual reassessment method to the rolling six design in pediatric oncology phase I trials. *Clin. Trials.* **8**, 361–369 (2011).
- 46 Doussau, A., et al. Dosefinding designs in pediatric phase I clinical trials: comparison by simulations in a realistic timeline framework. *Control. Clin. Trials.* **33**, 657–665 (2012).
- 47 Manji, A. et al. Evolution of clinical trial design in early drug development: systematic review of expansion cohort use in single-agent phase I cancer trials. *J Clin Oncol.* **31**, 4260-7 (2013).
- 48 Ensign, L.G., Gehan, E.A., Kamen, D.S., Thall, P.F. An optimal three-stage design for phase II clinical trials. *Stat Med.* **13**, 1727 (1994).
- 49 <https://clinicaltrials.gov/ct2/show/NCT02124772>
- 50 <https://clinicaltrials.gov/ct2/show/NCT02432274>
- 51 Moroz, V., Wilson, J.S., Kearns, P., Wheatley, K. Comparison of anticipated and actual control group outcomes in randomised trials in paediatric oncology provides evidence that historically controlled studies are biased in favour of the novel treatment. *Trials.* **15**, 481 (2014).
- 52 Moreno, L. et al. A randomised phase IIb trial of bevacizumab added to temozolomide ± irinotecan for children with refractory/relapsed neuroblastoma - BEACON-Neuroblastoma, a European Innovative Therapies for Children with Cancer (ITCC) - International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) trial. *J Clin Oncol.* **33**, (suppl; abstr TPS10082) (2015).
- 53 Mody, R. et al. Phase II randomized trial of irinotecan/temozolomide (I/T) with temsirolimus (TEM) or dinutuximab plus granulocyte colony stimulating factor (DIN/GMCSF) in children with refractory or relapsed neuroblastoma: A report from the Children's Oncology Group (COG). *J Clin Oncol.* **34** (suppl; abstr 10502) (2016).
- 54 Corbacioglu, S. et al. The RIST design: A molecularly targeted multimodal approach for the treatment of patients with relapsed and refractory neuroblastoma. *J Clin Oncol.* **31**:(suppl; 10017 abstr) (2013).
- 55 Kager, L. et al. The ENCCA-WP7/EuroSarc/EEC/PROVABES/EURAMOS 3rd European Bone Sarcoma Networking Meeting/Joint Workshop of EU Bone Sarcoma Translational Research Networks; Vienna, Austria, September 24–25, 2015. Workshop Report. *Clin Sarcoma Res.* **6**, 3 (2016).

- 56 Malempati, S. et al. Early results from Children's Oncology Group (COG) ARST08P1: Pilot studies of cixutumumab or temozolomide with intensive multiagent chemotherapy for patients with metastatic rhabdomyosarcoma. *J Clin Oncol.* **33**, (suppl; abstr 10015)(2015).
- 57 Jakacki, R. et al. Single-agent erlotinib versus oral etoposide in patients with recurrent or refractory pediatric ependymoma: a randomized open-label study. *J Neurooncol.* **129**, 131-8 (2016).
- 58 Yap, T.A., Sandhu, S.K., Workman, P., de Bono, J.S. Envisioning the future of early anticancer drug development. *Nat Rev Cancer.* **10**, 514-23 (2010).
- 59 Biomarkers Definition Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther.* **69**, 89-95 (2001).
- 60 Fouladi, M. et al. A phase I trial of MK-2206 in children with refractory malignancies: a Children's Oncology Group study. *Pediatr Blood Cancer.* **61**, 1246-51 (2014).
- 61 Moreno, L., et al. Phase I Trial of AT9283 (a Selective Inhibitor of Aurora Kinases) in Children and Adolescents with Solid Tumors: A Cancer Research UK Study. *Clin Cancer Res.* **21**, 267-73 (2015).
- 62 Smith, J.R., Moreno, L., Heaton, S.P., Chesler, L., Pearson, A.D., Garrett, M.D. Novel pharmacodynamic biomarkers for MYCN protein and PI3K/AKT/mTOR pathway signaling in children with neuroblastoma. *Mol Oncol.* **10**, 538-52 (2016).
- 63 Glade Bender, J.L. et al. Phase I pharmacokinetic and pharmacodynamic study of pazopanib in children with soft tissue sarcoma and other refractory solid tumors: a Children's Oncology Group Phase I Consortium report. *J Clin Oncol.* **31**, 3034-43 (2013).
- 64 Sedlacik, J., Winchell, A., Kocak, M., Loeffler, R.B., Broniscer, A., Hillenbrand, C.M. MR imaging assessment of tumor perfusion and 3D segmented volume at baseline, during treatment, and at tumor progression in children with newly diagnosed diffuse intrinsic pontine glioma. *Am J Neuroradiol.* **34**, 1450-5 (2013).
- 65 Schleiermacher, G. et al. Emergence of new ALK mutations at relapse of neuroblastoma. *J Clin Oncol.* **32**, 2727-34 (2014).
- 66 Hill, R.M. et al. Combined MYC and P53 Defects Emerge at Medulloblastoma Relapse and Define Rapidly Progressive, Therapeutically Targetable Disease. *Cancer Cell.* **27**, 72-84 (2015).
- 67 Carr-Wilkinson, J. et al. High Frequency of p53/MDM2/p14ARF Pathway Abnormalities in Relapsed Neuroblastoma. *Clin Cancer Res.* **16**, 1108-18 (2010).
- 68 Combaret, V. et al. Detection of tumor ALK status in neuroblastoma patients using peripheral blood. *Cancer Med.* **4**, 540-50 (2015).
- 69 Georger, B. et al. Molecular screening for cancer treatment optimization (MOSCATO 01) in pediatric patients: First feasibility results of a prospective molecular stratification trial. *J Clin Oncol.* **32**(suppl10500) (2014).
- 70 Worst, B.C. et al. Next-generation personalised medicine for high-risk paediatric cancer patients - The INFORM pilot study. *Eur J Cancer.* **65**, 91-101 (2016).
- 71 Harris, M.H. et al. Multicenter Feasibility Study of Tumor Molecular Profiling to Inform Therapeutic Decisions in Advanced Pediatric Solid Tumors: The Individualized Cancer Therapy (iCat) Study. *JAMA Oncol.* **2**, 608-615 (2016).
- 72 <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match>
- 73 Kearns, G.L., Abdel-Rahman, S.M., Alander, S.W., Blowey, D.L., Leeder, J.S., Kauffman, R.E. Developmental pharmacology – drug disposition, action, and therapy in infants and children. *N Engl J Med.* **349**, 1157-67 (2003)
- 74 Momper, J.D. et al. Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007. *JAMA Pediatr.* **167**, 926-932 (2013)
- 75 <https://clinicaltrials.gov/ct2/show/NCT01353625>
- 76 <https://clinicaltrials.gov/ct2/show/NCT02304458>
- 77 <https://clinicaltrials.gov/ct2/show/NCT01524926>

- 78 Voss, S.D. et al. Growth plate abnormalities in pediatric cancer patients undergoing phase 1 anti-angiogenic therapy: a report from the Children's Oncology Group Phase I Consortium. *Pediatr Blood Cancer*. **62**,45-51 (2015).
- 79 Kimura, H., Ng, J.M., Curran, T. Transient inhibition of the Hedgehog pathway in young mice causes permanent defects in bone structure. *Cancer Cell*. **13**,249–60 (2008).
- 80 Geoerger, B. et al. A phase I/II study of LDE225, a smoothened antagonist, in pediatric patients with recurrent medulloblastoma or other solid tumors. *J Clin Oncol* **30**, (suppl; abstr 9519) (2012).
- 81 Gajjar, A. et al. Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: a pediatric brain tumor consortium study. *Clin Cancer Res*. **19**, 6305-12 (2013).
- 82 <https://clinicaltrials.gov/ct2/show/NCT01125800>
- 83 Goteke, V.K.R. et al. An anthropometric study in children with chronic myeloid leukemia on imatinib. *J Clin Oncol*. **30**, (suppl; abstr 6554) (2012).
- 84 Shima, H. et al. Distinct impact of imatinib on growth at prepubertal and pubertal ages of children with chronic myeloid leukemia. *J Pediatr*. **159**, 676-81 (2011).
- 85 PanCare. Pancare, Pan-European Network for Care of Survivors after childhood and adolescent cancer. 2016. www.pancare.eu (accessed 27 June 2016).
- 86 Dupont, J.C., Pritchard-Jones, K., Doz, F. Ethical issues of clinical trials in paediatric oncology from 2003 to 2013: a systematic review. *Lancet Oncol*. **17**,e187-97 (2016).
- 87 Hampson, L.V. et al. Elicitation of expert prior opinion: application to the MYPAN trial in childhood polyarteritis nodosa. *PLoS One*. **10**, :e0120981 (2015).
- 88 Trippett, T.M. et al. Phase I and pharmacokinetic study of cetuximab and irinotecan in children with refractory solid tumors: a study of the pediatric oncology experimental therapeutic investigators' consortium. *J Clin Oncol*. **27**, 5102–8 (2009)
- 89 Glade Bender, J.L. et al. Phase I trial and pharmacokinetic study of bevacizumab in pediatric patients with refractory solid tumors: a Children's Oncology Group Study. *J Clin Oncol*. **26**, 399–405 (2008)
- 90 Kieran, M.W. et al. Phase 1 study of dabrafenib in pediatric patients with relapsed or refractory BRAF V600E high- and low-grade gliomas, Langerhans cell histiocytosis, and other solid tumors. *J Clin Oncol*. **33** (suppl; abstr 10004) (2015).
- 91 Daw, N.C. et al. Phase I and pharmacokinetic study of gefitinib in children with refractory solid tumors: a Children's Oncology Group Study. *J Clin Oncol*. **23**, 6172–80. (2005)
- 92 Locatelli, F. et al. Phase 1/2 Study in Pediatric Patients with Relapsed/Refractory B-Cell Precursor Acute Lymphoblastic Leukemia Receiving Blinatumomab Treatment. *Blood*. **124**, 2292 (2014).

Figure and Table Captions

Figure 1: Schema of proposed design of early phase clinical trial in children controlling for toxicity and testing whether activity is above 30% and not below 10% in three-stage (Ensign) designs.

- a) Molecularly targeted drug / immunotherapeutic without serious, dose-related toxicities and a wide therapeutic index
- b) Molecularly targeted drug / immunotherapeutic with serious, dose-related toxicities and a narrow therapeutic index

Table 1- Review of 92 published paediatric dose finding clinical trials in oncology and haematology between 2009 and 2015

Table 2: Dose finding designs

Table 3: Recommendations for Early Phase Studies in Children based on Findings from Studies in Adults

Table 4: Summary of recommendations

Table 5: Biomarkers

Text box 1: Definition of early phase clinical trial

Text box 2: Precision medicine in children and adolescents

Text box 3: Ethical aspects related to paediatric oncology early phase clinical trials

Metric	Median	Range
Age at enrolment (years)	10	1-30
Dose levels in escalation cohort	3	1-10
Number of patients enrolled in escalation cohort	18	2-67
Number of patients enrolled in study	24	6-79
Median duration of the 92 trials (including escalation part and expansion cohorts/phase II) (months)	30	5-92
Median duration of the 54 trials that only had escalation cohorts (months)	27.5	5-73

Table 1- Review of 92 published paediatric dose finding clinical trials in oncology and haematology between 2009 and 2015 with 112 escalation cohorts (some trials had several parallel dose-escalation cohorts)¹⁹

Definition of early phase clinical trial

An early phase clinical trial has two principal components, i) a dose confirmation or escalation confirmation phase in which the toxicity profile, the RP2D and preliminary pharmacokinetics are determined ii) expansion cohorts where additional pharmacokinetic, pharmacodynamic and safety data are obtained and importantly early signals of anti-tumour activity. “Early phase clinical trial” is a term that encompasses the first stages of the clinical development of a drug to define its dose, toxicity profile, biomarkers, and early signals of anti-tumour activity before transitioning to “late stage” phase II or III trials aimed at determining the drug’s efficacy.

Text box 1: Definition of early phase clinical trial

Precision medicine in children and adolescents

- Precision medicine can be defined as therapeutic decisions guided by the molecular or genomic features of a tumour rather than on the basis of clinicopathological features.
- Central to precision medicine is understanding the molecular pathways, biology and key drivers of paediatric malignancies, focussing on aberrations that demonstrate a proof of “tumour dependence”.
- Recent sequencing has shown that the genetic and epigenetic repertoire of driver mutations in specific childhood malignancies differs from more common adult-type malignancies.
- The number of non-synonymous coding mutations in childhood tumours is on average about a hundred-fold lower than in adult malignancies.
- Information on the presence of actionable target mutations is the most easily obtained data; determination of the functional relevance of identified targets for tumour cell survival and the relevance of complicated tumour-host interactions is a more challenging task.
- Currently, precision medicine in paediatric oncology focuses on actionable target mutations, particularly those for which there are available drugs developed for adult cancers (e.g., ALK or BRAF). Initial investigations suggest that these can be detected in about 50% of tumours⁶⁶⁻⁶⁹.
- The major challenges currently in implementing precision medicine in paediatric oncology are that the focus is only on actionable mutations, the presence of multiple alterations and the limited access to targeted agents.
- As the driver mutations in childhood malignancies differ from more common adult-type malignancies, many recently developed adult cancer agents do not target childhood cancers. Therefore, there is a paucity of targeted cancer drugs addressing paediatric cancer oncogenic drivers. Developing drugs to target genomic alterations in childhood malignancies is a key challenge to successfully applying precision medicine principles.
- The multiple agent ITCC European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours (ESMART) study (NCT02813135) is not 100% enriched and restricted to patients with pre-defined molecular alterations. On the contrary, a secondary objective is to compare outcomes of patients with molecular abnormalities, matching the treatment to those without druggable targets.
- Although significant progress has been made, drug development for children with cancer is still focused on adult conditions. A recent analysis suggests that 73% of new anti-cancer agents, whose evaluation in children was waived, had a target or MoA that would warrant paediatric development based on existing molecular data.

- We propose that prioritisation of targeted agents is facilitated by Paediatric Strategy Forums. The output of a Paediatric Strategy Forum would provide a perspective that that will enable all stakeholders to have an overview of the landscape, which will facilitate sharing of information and advance learning, which will help inform subsequent decisions.
- In a Mechanism of Action approach to development of drugs for children and adolescents with cancer, all hallmarks of cancer including epigenetics and immunotherapy are targeted.

Text box 2: Precision medicine in children and adolescents

Ethical aspects related to paediatric oncology early phase clinical trials⁸³

- Ethics should guide all aspects of early phase clinical trials within the legal framework²⁵. Specific aspects related to paediatric early phase clinical trials are:
 - Therapeutic intent
 - Ancillary studies and invasive biopsies
 - Consent/Assent
 - Minimisation of all risks and distress to the patient
- The scientific information gained from an early phase clinical trial must be weighed against ethical aspects.
- Ethical issues can be broadly grouped into four areas: research ethics, legal and ethical consistency, professionalism and consent.
- That the research objectives and underlying scientific rationale of the research is strong is of pivotal importance.
- Therapeutic intent is central to early phase clinical trials in paediatric malignancy.
- An early phase clinical trial is an option to be proposed to the patient and his / her parents.
- Availability of tumour material at the time of enrolment in an early phase trial will enable the maximal knowledge to be obtained from the study. Generally, using archival tumour from an earlier presentation is inappropriate, as it is well documented that clonal evolution occurs in the vast majority of cases. Data from a tumour biopsy could identify potential molecularly targeted drugs that could be utilised in a precision medicine strategy with molecular enrichment and predictive biomarkers. The need for tumour sampling immediately prior to study entry needs to be placed within the context of the agent being studied, the objectives of the clinical trial, the ethical justifications for tumour sampling, the accessibility of tumour material and the clinical status of the individual patient.
- The inclusion of ancillary/biological studies (tumour analysis and pharmacodynamic studies) increases the scientific value of early phase clinical trials, and thus, the future use of the drug. For instance, to understand issues such as genetic variability of drug metabolism or mechanisms of drug resistance are central questions, which should be studied as early as possible during a drug's development.
- Much information regarding pharmacodynamic biomarkers can be obtained non-invasively or by blood sampling. We believe that a way forward should be developed so that early drug development can be efficient and based on scientific information through pharmacodynamic and biological studies whilst abiding by ethical constraints.

- Liquid biopsies have an important potential future role as they may provide relevant molecular diagnostic, prognostic, predictive information and might be used during treatment to predict response / resistance to treatment with minimal distress to the patients.
- Starting to evaluate drugs in the paediatric population at doses substantially below those already established to be active in adults raises ethical concerns, as therapeutic intent is central to studies in children. An equivalent dose of the minimum active target exposure should be mandatory for the paediatric starting dose for most agents.
- All care should be taken during the design of a new protocol to minimize distress to patients, including: the number of hospital visits, uncomfortable tests, frequent sedations, painful procedures and the number of diagnostic procedures.

Text box 3: Ethical aspects related to paediatric oncology early phase clinical trials